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09/990,185	11/21/2001	Krzysztof Palczewski	P-NS 4970	1224

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CATHRYN CAMPBELL
CAMPBELL & FLORES LLP
4370 LA JOLLA VILLAGE DRIVE
7TH FLOOR
SAN DIEGO, CA 92122

EXAMINER	
ANGELL, JON E	
ART UNIT	**PAPER NUMBER**
1635	9

DATE MAILED: 07/30/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/990,185	Applicant(s) PALCZEWSKI ET AL.	
	Examiner J. Eric Angell	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-38* is/are pending in the application.

4a) Of the above claim(s) *28,29,37 and 38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27 and 30-36* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

1. This Action is in response to the communication filed on 4/7/03, as Paper No. 8. Claims 1-38 are currently pending in the application and are addressed herein.

Election/Restrictions

2. Applicants pointed out the former Examiner's typographical error which indicated Group I consisted of claims 1-27, 30 and 36, rather than 1-27 and 30-36. Group I should consist of claims 1-27 and 30-36.

3. Applicant's election with traverse of Group I (claims 1-27 and 30-36) in Paper No. 8 is acknowledged. The traversal is on the ground(s) that there is no serious search burden because the search of Group I would allegedly include searches for the other groups. This is not found persuasive because the three groups have different classifications—prima facie evidence of a serious search burden.

The requirement is still deemed proper and is therefore made FINAL.

Claims 28, 29, 37 and 38 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 8 (filed 4/7/03).

Claims 1-27 and 30-36 are examined herein.

Specification

4. The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, for example see p.7, line 30. Applicant is required to delete all embedded hyperlinks and/or other form of browser-executable code in response to this Action. See MPEP § 608.01.

Claim Rejections - 35 USC § 112

5. Claims 1-27 and 30-36 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Factors to be considered in determining whether a disclosure meets the enablement requirement of 35 USC 112, first paragraph, have been described by the court in *In re Wands*, 8 USPQ2d 1400 (CA FC 1988).

Wands states on page 1404,
"Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims."

6. The instant claims are drawn to a gene targeting construct, a vector comprising the construct, a mouse cell comprising the construct and a gene disrupted mouse comprising the construct. It is noted that the only use for the construct, vector and mouse cell contemplated by the specification is for making a transgenic mouse comprising a functional disruption of one or

both endogenous rhodopsin gene alleles and which expresses a polypeptide of interest comprising an rod outer segment (ROS) targeting signal.

7. The specification indicates different possible uses for the transgenic mouse, including expressing a large amount of the transgenic protein of interest such that it accumulates in the rod cells of the eye, wherein the transgenic protein can be purified from rod cells. Also, the specification contemplates expressing G-protein coupled receptors (GPCR) as the transgenic protein so that the transgenic GPCR can be used in studies, such as screening assays to identify modulators of GPCR activity. However, neither the specification nor the instant claims indicate that the transgenic mouse has any particular phenotype. Furthermore, the specification has no working examples demonstrating that the transgenic mouse has been made and has a particular phenotype.

The specification fails to provide an enabling disclosure for the preparation of the claimed transgenic mice exhibiting a particular phenotype. Because the specification discloses no phenotype for the transgenic mice, undue experimentation would have been required for one of skill in the art to make and/or use the claimed invention. To this end, the specification does not provide guidance for any particular phenotype for the claimed transgenic mice, other than the anticipated expression of the transgene.

Note that the mere capability to perform gene transfer in a mouse is not enabling because a desired phenotype cannot be predictably achieved by simply introducing transgene constructs of the types recited in the claims. While gene transfer techniques are well developed for a number of species, and particularly for the mouse, methods for achieving the desired level of

transgene expression in appropriate tissues are less well established. The introduction of DNA into the mammalian genome can ordinarily be achieved most reliably by microinjection or retrovirus-mediated gene transfer. However, the state of the art for transgenics is unpredictable because the method of gene transfer typically relies on random integration of the transgene construct. Insertional inactivation of endogenous genes and position effects [see Ryan *et al.*, **Sem. Neph.** 22:154-160, 2002] can dramatically influence the phenotype of the resultant transgenic animal. Ryan states that methods such as pronuclear injection or gene targeting by homologous recombination are still limited by several unpredictabilities, including differences in transgene copy number and position of integration into the genome. Furthermore, Ryan teaches, "The location of integration can have dramatic effects on the expression of a transgene. Called the position effect, transcriptional regulatory sequences at or near the insertion site can strongly influence your transgene, even impart a new set of instructions. " [See p. 155, 2nd column].

In the instant case the targeting construct is designed to insert the gene of interest into the rhodopsin gene (either one or both alleles of rhodopsin). The inserted gene construct would "knock-out" the rhodopsin allele it integrated into. The integrated transgene then theoretically be under the control of the rhodopsin gene expression elements (i.e. promoters, enhancers etc.). Furthermore, the gene of interest comprises a ROS targeting sequence in order to theoretically target the expressed transgenic polypeptide to the rod outer segments where the transgenic protein can be purified or used in assays. However, targeting the construct to the rhodopsin gene may present caveats. For instance, integration of the transgene into both alleles of the rhodopsin gene would create a rhodopsin knockout mouse. Lem et al. **[PNAS Vol. 96p. 736-741; 1999]** teaches,

> "Retinas in mice lacking both opsin alleles initially developed normally, except that rod outer segments failed to form. Within months of birth, photoreceptor cells degenerated completely." (See abstract).

Therefore, integration of transgene into both rhodopsin alleles could result in a mouse that fails to develop rod outer segments. This would create a problem for expressing the transgene having the ROS targeting sequence. It is unclear how the transgene would be expressed and targeted in this instance. Furthermore, without actually making the transgenic mouse there is no guarantee that the transgene will be expressed at the desired level or that the transgenic polypeptide would be targeted to the ROS, as desired.

Additionally, expression of the transgene and the effect of transgene expression on the phenotype of the transgenic animal depend upon the particular gene construct used, to an unpredictable extent. This is supported by Holschneider *et al.* [**Int J. Devl. Neuroscience** 18:615-618, 2000] who state that the, "knocking out or insertion of a single gene may result in no phenotypic change. This may be the case, in particular, if there exist gene redundancy mechanisms whose presence may prevent abnormal phenotypes from becoming masked. Conversely, single genes are often essential in a number of different behaviors and physiologic processes. Hence, ablation of an individual gene may prove so drastic as to be lethal, or so widespread as to create an amalgam of phenotypes whose interpretation becomes confounded by the interactions of the various new physiologic changes or behaviors." [See p. 615, col. 1-2]. Holschneider discusses various factors that contribute to the resulting phenotype of transgenic mice, including compensatory systems which may be activated to mask the resulting phenotype, these compensatory changes may be due to the differential expression of another gene, which

may be regulated by the downstream product of the ablated gene, as well as the variability in phenotypic characterization due to particular mouse strains [see p. 616, 1st column].

Given that specific phenotypic alterations cannot be predictably achieved by merely transferring a gene of interest into an animal, specific guidance must be provided to enable the instant invention. The specification must teach those skilled in the art how to make and use the full scope of the claimed invention without undue experimentation. The claims cover the use of the claimed transgenic mice in methods of producing and purifying transgenic protein as well as method for screening compounds, but the specification does not enable this use.

Considering that the only contemplated use for the targeting construct, the vector, and the cell comprising the construct is for making the transgenic mouse, these claims are also rejected as not being enabled because the only use contemplated is not enabled.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to J. Eric Angell whose telephone number is (703) 605-1165. The examiner can normally be reached on M-F (8:00-4:30).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader can be reached on (703) 308-0447. The fax phone numbers for

the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

J. Eric Angell
July 25, 2003

Anne-marie Falk

ANNE-MARIE FALK, PH.D
PRIMARY EXAMINER